

常规超声联合超微血流成像评估血友病性滑膜炎在 骨软骨损伤风险预测中的应用价值

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[摘要] 目的:使用常规超声联合超微血流成像(SMI)评估血友病性滑膜炎,探讨其对骨软骨损伤的预测价值。方法:纳入 2023 年 1 月—2023 年 12 月于我院就诊的血友病 A 患者 57 例,受累关节共计 155 例,对受累关节行常规超声及关节滑膜 SMI 检查,分析一般临床资料、常规超声特征、SMI 参数与骨软骨损伤的相关性,比较骨软骨损伤关节与无骨软骨损伤关节一般临床资料、常规超声特征、SMI 参数的差异,分析骨软骨损伤的独立危险因素,绘制受试者工作特征(ROC)曲线,获取各危险因素截断值,检验其对骨软骨损伤的预测价值。结果:在 155 例受累关节中,有骨软骨损伤关节 108 例,无骨软骨损伤关节 47 例。常规超声所测滑膜厚度与软骨评分、骨评分呈显著正相关($r=0.66, 0.69$);SMI 参数滑膜血管指数(VI)与软骨评分、骨评分呈显著正相关($r=0.61, 0.67$)。多因素 Logistic 回归分析显示,患者年龄、滑膜厚度、滑膜 VI 是骨软骨损伤的独立危险因素,ROC 曲线显示,其预测骨软骨损伤的曲线下面积分别为 0.74、0.90、0.91。基于截断值年龄 ≥ 19 岁、关节滑膜厚度 ≥ 3.95 mm、滑膜 VI $\geq 2.35\%$ 提示骨软骨损伤,其敏感性分别为 85.0%、85.8%、76.7%,特异性分别为 60.0%、85.7%、97.1%。结论:常规超声联合 SMI 评估血友病性滑膜炎能较好地预测骨软骨损伤的风险,对早期监测和干预滑膜炎、预防骨软骨损伤具有重要价值。

[关键词] 滑膜炎;骨折,软骨;超声检查

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The value of conventional ultrasound combined with superb microvascular imaging in assessing hemophilic synovitis for predicting the risk of osteochondral injury

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Abstract: Objective: Using conventional ultrasound and superb microvascular imaging(SMI) to assess hemophilic synovitis, exploring their predictive value for osteochondral injury. **Methods:** Fifty-seven hemophilia A patients visited our hospital from January 2023 to December 2023, with a total of 155 affected joints enrolled. Conventional ultrasound and synovial SMI examinations were performed on the affected joints. The study analyzed the correlation between clinical data, conventional ultrasound and SMI parameters with osteochondral injury, and compared the differences in clinical data, conventional ultrasound characteristics, and SMI parameters between joints with osteochondral injury and those without. The independent risk factors for osteochondral injury were analyzed, and the receiver operating characteristic (ROC) curve was plotted to obtain cutoff values for each risk factor and evaluate their predictive value for osteochondral injury. **Results:** Among 155 affected joints, there were a total of 108 joints with osteochondral injury and 47 joints without osteochondral injury. The synovial thickness measured by conventional ultrasound was significantly positively correlated with cartilage and bone scores ($r=0.66, 0.69$); the SMI parameter synovial vascular index (VI) was significantly positively correlated with cartilage and bone scores ($r=0.61, 0.67$). Multivariate Logistic regression analysis showed that patient age, synovial thickness, and synovial VI were independent risk factors for osteochondral injury. The ROC curve showed that the area under the curve for predicting osteochondral injury was 0.74, 0.90, and 0.91, respectively. Based on the cutoff values of age ≥ 19 years, joint synovial thickness ≥ 3.95 mm, and synovial VI $\geq 2.35\%$, osteochondral injury was indicated, with sensitivities of 85.0%, 85.8% and 76.7%, and specificities of 60.0%, 85.7% and 97.1%, respectively. **Conclusion:** The assessment of hemophilic synovitis using conventional ultrasound combined with SMI can effectively predict the risk of osteochondral injury. This has significant value for early monitoring and intervention of synovitis and the prevention of osteochondral injury.

Key words: Synovitis; Fractures, Cartilage; Ultrasonography

血友病是一组 X 染色体连锁隐性遗传出血性疾病,由于凝血因子 VIII(FVIII)或凝血因子 IX(FIX)缺乏,导致凝血功能障碍。血友病患者会出现承重关节反复出血^[1],反复出血会导致关节滑膜炎、增生和

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新生血管形成,新生血管脆性较大将导致滑膜更易出血,形成出血-滑膜炎-出血恶性循环,进展为慢性滑膜炎,而滑膜炎因子及血液中细胞因子将进一步导致不可逆性软骨及骨损伤,因此,滑膜炎是血友病患者骨软骨损伤的开始^[2]。同时,研究显示,滑膜新生血管重构是足量凝血因子治疗下关节再出血的重要原因^[3-4]。因此,早期、准确监测血友病患者关节滑膜炎及滑膜新生血管,在骨软骨损伤出现前及时干预,对预防关节畸形具有重要意义。超微血流成像(Superb microvascular imaging, SMI)为近年快速发展的超声新技术,已有多项研究证实了其在滑膜新生血管评估中具有较好的应用价值^[5-6]。本研究拟采用常规超声联合 SMI 评估血友病患者关节滑膜病变,探讨其与骨软骨损伤的相关性及对骨软骨损伤的预测价值,为治疗方案早期调整提供依据。

1 资料与方法

1.1 研究对象

纳入 2023 年 1 月—2023 年 12 月于我院就诊的血友病 A 患者共 57 名,受累关节共 155 例,患者均为男性,治疗方案均为规范化凝血因子预防治疗^[7]。入组标准:符合中华医学会血液学分会血栓与止血学组制定的血友病诊断标准,确诊为血友病 A^[7],并经常规超声检查为有关节受累者。排除标准:抑制物阳性患者;合并其他关节疾病,如化脓性关节炎、类风湿性关节炎等;有关节手术史;合并其他凝血功能障碍疾病,如获得性血友病、血小板减少相关疾病等。

1.2 仪器与方法

采用 Aplio I700 彩色多普勒超声诊断仪,高频线阵探头,频率 5~14 MHz,选择肌肉骨骼模式,行关节常规超声检查,SMI 评估关节滑膜血流。

记录患者的年龄、身高、体质量、受累关节及近两年关节出血次数。

常规超声检查:血友病关节超声评估量表(HEAD-US)^[8]为血友病性关节病变的首选评估系统。本研究根据中国版 HEAD-US(HEAD-US-C)^[9]评估受累关节。其具体评分标准:关节积液评分:无积液记 0 分,少量积液记 1 分,中量积液记 2 分,大量积液记 3 分;滑膜厚度测量及评分:无滑膜增厚记 0 分,轻度或中度滑膜增厚记 1 分,重度滑膜增厚记 2 分;使用能量多普勒(Power Doppler flow imaging, PDFI)对滑膜内血流信号进行评分:无血流信号记 0 分,感兴趣区血流信号<3 处记 1 分,≥3 处记 2 分;关节软骨评分:正常软骨记 0 分,靶表面<25%的软骨缺失记 1 分,25%~≤50%的软骨缺失记 2 分,>50%~<100%的软骨缺失记 3 分,完全消失记 4 分;骨评分:正常

骨记 0 分,软骨下骨轻度不规则或不伴关节周围小骨赘记 1 分,明显不规则和/或显著关节周围骨赘形成记 2 分。

SMI 检查:于 PDFI 所示滑膜血流信号最丰富切面,切换至 SMI 模式,根据 Adler 半定量评分法^[10]对滑膜血流进行分级:0 级,滑膜内无血流信号;1 级,滑膜内见 1~2 处点状血流信号;2 级,滑膜内见 3~4 处短线状血流信号,且分布<1/2 滑膜面;3 级,滑膜内见树枝状血流信号,且分布≥1/2 滑膜面。同时,于血流信号最丰富处勾画感兴趣区域(Region of interest, ROI),ROI 面积均取 0.75 cm²,计算血管指数(Vascular index, VI),定量分析滑膜血流。

1.3 统计学方法

应用 SPSS 24.0 软件进行统计学分析,计量资料用均数±标准差($\bar{x}\pm s$)表示,组间比较采用独立样本 *t* 检验。计数资料用频数和百分比表示,组间比较采用 χ^2 检验。采用 Spearman 相关性分析评估一般临床资料及各超声指标与软骨评分、骨评分的相关性。根据 HEAD-US-C,软骨评分与骨评分总和大于 0 分即为有骨软骨损伤,将患者分为骨软骨损伤组与无骨软骨损伤组,采用单因素及多因素 Logistic 回归分析筛选骨软骨损伤的独立危险因素,绘制受试者工作特征(ROC)曲线,获取各危险因素截断值,检验其对骨软骨损伤的预测价值, $P<0.05$ 为差异有统计学意义。

2 结果

2.1 一般临床资料

57 名血友病 A 患者中,平均年龄为(28.70±11.52)岁。155 例受累关节中,膝关节 51 例,踝关节 60 例,肘关节 44 例,关节平均出血次数为(3.72±5.40)次。有骨软骨损伤关节 108 例,无骨软骨损伤关节 47 例。

2.2 相关性分析结果

在一般临床资料中,患者年龄、出血次数与软骨评分、骨评分呈轻度正相关($r=0.18、0.24、0.21、0.29$,均 $P<0.05$),患者身高、体质量与软骨评分、骨评分无相关性(均 $P>0.05$);在常规超声参数中,滑膜厚度与软骨评分、骨评分呈显著正相关($r=0.66、0.69$,均 $P<0.01$),关节积液评分、PDFI 血流评分与软骨评分、骨评分呈轻度正相关($r=0.20、0.27、0.55、0.57$,均 $P<0.05$);在 SMI 参数中,SMI 血流分级、VI 与软骨评分、骨评分呈显著正相关($r=0.60、0.65、0.61、0.67$,均 $P<0.01$)。

2.3 两组间单因素分析结果

在一般临床资料的比较中,骨软骨损伤组患者的年龄((30.72±10.95)岁)显著大于无骨软骨损伤组

((21.82±10.92)岁)($P<0.01$),骨软骨损伤组关节出血次数((4.31±5.98)次)显著大于无骨软骨损伤组((1.68±1.16)次)($P<0.05$);身高、体质量在两组比较中无统计学差异(均 $P>0.05$)。在常规超声参数及 SMI 参数的比较中,骨软骨损伤组滑膜厚度((6.73±3.13) mm)显著大于无骨软骨损伤组((2.10±2.41) mm)

($P<0.01$),骨软骨损伤组滑膜 VI((6.56±7.94)%)显著大于无骨软骨损伤组((0.58±1.70)%)($P<0.01$),滑膜 PDFI 血流评分、SMI 血流分级在两组比较中差异具有统计学意义(均 $P<0.01$)(图 1,2),关节积液评分在两组比较中差异无统计学意义($P>0.05$)。

2.4 骨软骨损伤独立危险因素及截断值分析

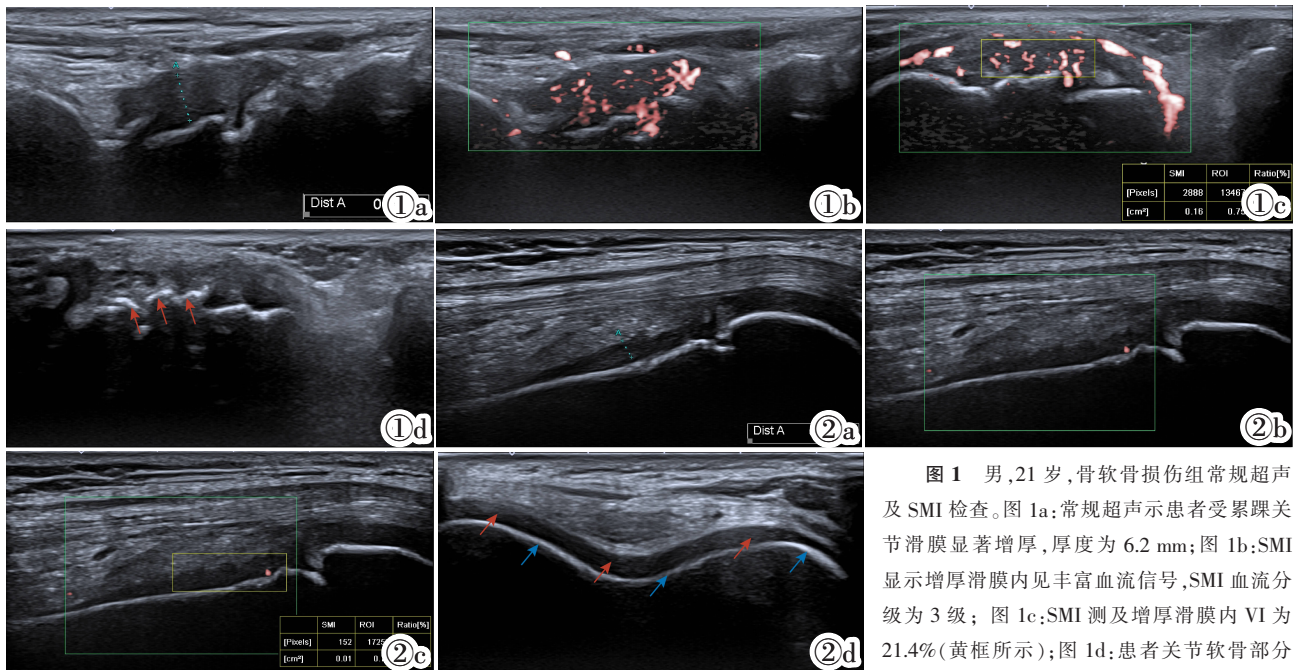


图 1 男,21 岁,骨软骨损伤组常规超声及 SMI 检查。图 1a:常规超声示患者受累踝关节滑膜显著增厚,厚度为 6.2 mm;图 1b:SMI 显示增厚滑膜内见丰富血流信号,SMI 血流分级为 3 级;图 1c:SMI 测及增厚滑膜内 VI 为 21.4%(黄框所示);图 1d:患者关节软骨部分消失,骨皮质表面不光滑,不连续伴多发骨赘形成(红色箭头所示)。**图 2** 男,14 岁,无骨软骨损伤组常规超声及 SMI 检查。图 2a:常规超声示患者膝关节滑膜轻度增厚,厚度为 2.5 mm;图 2b:SMI 显示增厚滑膜内见点状血流信号,SMI 血流分级为 1 级;图 2c:SMI 测及增厚滑膜内 VI 为 0.9%(黄框所示);图 2d:软骨及骨皮质表面光滑,连续,未见受损(红色箭头示极低回声关节软骨,蓝色箭头示强回声骨皮质表面)。

Figure 1. Male, 21 years old, conventional ultrasound and SMI examination of osteochondral injury group. Figure 1a: Conventional ultrasound shows synovium thickening in the affected ankle joint, with a thickness of 6.2 mm; Figure 1b: SMI shows abundant blood flow signals observed in the thickened synovium, SMI blood flow grade is 3; Figure 1c: VI within the thickened synovium measured by SMI is 21.4%(shown in the yellow box); Figure 1d: Partial disappearance of the joint cartilage, the bone cortex surface is rough and discontinuous with multiple osteophyte formation (indicated by red arrows). **Figure 2.** Male, 14 years old, conventional ultrasound and SMI examination of non-osteochondral injury group. Figure 2a: Conventional ultrasound shows mild synovium thickening in the knee joint, with a thickness of 2.5 mm; Figure 2b: SMI shows punctate blood flow signals observed in the thickened synovium, SMI blood flow grade is 1; Figure 2c: VI within the thickened synovium measured by SMI is 0.9%(shown in the yellow box); Figure 2d: The surface of the cartilage and bone cortex is smooth and continuous, with no damage observed (red arrow indicates the hypoechoic joint cartilage, blue arrow indicates the hyperechoic bone cortex surface).

将两组比较中有统计学差异的指标纳入多因素 Logistic 回归分析,结果显示患者年龄(OR 值:1.07, 95%CI:1.00~1.14, $P<0.05$)、关节滑膜厚度(OR 值:1.92, 95%CI:1.29~2.88, $P<0.01$)、滑膜 VI(OR 值:2.46, 95%CI:1.04~5.83, $P<0.05$)是骨软骨损伤的独立危险因素。以患者是否存在骨软骨损伤为标准,绘制患者年龄、滑膜厚度、滑膜 VI 的 ROC 曲线,其曲线下面积分别为 0.74(95%CI:0.63~0.84, $P<0.01$)、0.90(95%CI:0.84~0.97, $P<0.01$)、0.91(95%CI:0.86~0.96, $P<0.01$)(图 3)。当患者年龄截断值取 19 岁、滑膜厚度截断值取 3.95 mm、滑膜 VI 截断值取 2.35%时,约登指数最高,提示具有骨软骨损伤风险,敏感性分别

为 85.0%、85.8%、76.7%,特异性分别为 60.0%、85.7%、97.1%。

3 讨论

慢性滑膜炎是血友病患者骨软骨损伤的开始^[1],研究显示,即使在足量凝血因子预防治疗下,关节滑膜炎仍与血友病患者关节健康直接相关^[2]。因此,早期、准确监测滑膜炎及滑膜新生血管,及时调整治疗方案,为血友病患者提供凝血因子替代治疗为主、抗滑膜炎症及新生血管等为辅的个体化治疗,对于预防骨软骨损伤、提高患者生存质量具有重要意义。

大量研究已证实了常规超声在检测血友病患者

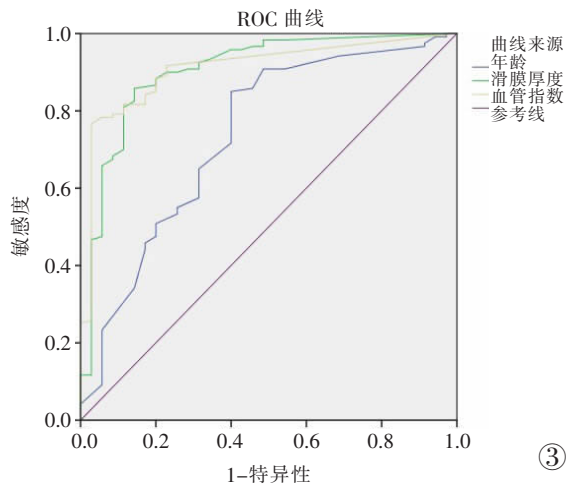


图3 独立危险因素的ROC曲线。患者年龄的AUC为0.74(95%CI:0.63~0.84, $P<0.01$) (蓝线所示)、滑膜厚度的AUC为0.90(95%CI:0.84~0.97, $P<0.01$) (绿线所示)、VI的AUC为0.91(95%CI:0.86~0.96, $P<0.01$) (黄线所示)。

Figure 3. ROC curves of independent risk factors. The AUC of age is 0.74 (95%CI: 0.63~0.84, $P<0.01$) (shown by the blue line); the AUC of synovial thickness is 0.90 (95%CI: 0.84~0.97, $P<0.01$) (shown by the green line); the AUC of synovial vascular index is 0.91(95%CI: 0.86~0.96, $P<0.01$) (shown by the yellow line).

关节滑膜增生中的重要价值^[13-14]。而在对滑膜血流及新生血管的检测中,对比增强核磁共振(Dynamic contrast-enhanced MRI, DCE-MRI)检查为金标准^[15],但检查耗时长,费用高昂,使用受限;超声造影(Contrast enhanced ultrasound, CEUS)能较好显示组织微循环,对滑膜微细血流的显示与病理检查具有良好相关性^[6],但需经静脉注射造影剂,在多关节长期监测中使用受限;SMI可以方便、快捷、无创地显示组织内低速血流及微细血流,研究显示,在对关节滑膜低速血流的检测中,SMI的敏感性优于PDFI^[17-18],与MRI具有较好的相关性^[6],与CEUS的敏感性相当^[5,19]。因此,SMI可以作为检测血友病患者滑膜新生血管的理想方式。

目前尚无研究探讨SMI量化评估血友病患者滑膜新生血管在骨软骨损伤风险预测中的应用价值。本研究首次使用常规超声联合SMI量化评估血友病患者滑膜增生及滑膜新生血管,探讨其与骨软骨损伤的关系,结果显示,常规超声所测关节滑膜厚度及SMI所测滑膜VI与软骨评分、骨评分显著相关,且是骨软骨损伤的独立危险因素,在血友病性滑膜炎与关节健康的欧洲专家共识中亦指出,滑膜炎是关节骨软骨损伤的主要原因^[20],而在本研究中,常规超声联合SMI较好地实现了对血友病性滑膜炎的量化评估,避免了血流分级等半定量指标的主观性,同时可作为骨软骨损伤风险的监测指标,为血友病患者治疗方案的调整提供依据。

在对一般临床资料的分析中,本研究结果显示,

患者年龄是骨软骨损伤的独立危险因素。Leissinger等^[21]、De la Corte-Rodriguez等^[22]的研究亦显示,血友病患者关节功能状态随着年龄增加而降低,也可能是因为随着经济发展和预防治疗的普及,许多年轻患者从出生即接受凝血因子预防治疗,较大地降低了出血机率,因此其关节状态优于年龄较大的患者。同时,本研究结果显示,关节年出血次数不是骨软骨损伤的独立危险因素,这是因为即使在规范预防治疗下,部分患者仍存在无症状性亚临床出血^[23],导致其临床出血次数与关节状态并不相关^[24],再次说明超声在亚临床出血监测中十分必要。

基于上述独立危险因素,通过ROC曲线分析,本研究探讨了常规超声联合SMI评估血友病性滑膜炎对骨软骨损伤的预测价值,并获取了截断值,提示其能较好地预测骨软骨损伤风险,同时在滑膜病变的定期监测中,应将滑膜厚度控制在3.95 mm以下,滑膜VI控制在2.35%以下,这为血友病性滑膜炎的早期干预和治疗策略早期调整提供了依据,有利于打破其向不可逆性骨软骨损伤发展的病变进程,对于预防关节畸形、提高患者生存质量具有重要意义。同时,应关注年龄对血友病患者关节功能的影响,对于19岁以上、病程较长的患者应采取更加综合、个体化的治疗方案。

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